(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 January 2003 (16.01.2003)

PCT

(10) International Publication Number
WO 03/004505 A1

(51) International Patent Classification[7]: C07F 15/00, A61K 31/28

(21) International Application Number: PCT/CH02/00358

(22) International Filing Date: 2 July 2002 (02.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CH01/00414 2 July 2001 (02.07.2001) CH
PCT/CH01/00618 15 October 2001 (15.10.2001) CH

(71) Applicant *(for all designated States except US)*: **DEBIOPHARM S.A.** [CH/CH]; Avenue des Terreaux 17, case postale 211, CH-1000 Lausanne 9 (CH).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **IBRAHIM, Houssam** [CH/CH]; 16, ch. des Etournelles, CH-1255 Veyrier (CH).

(74) Agent: **ROLAND, André**; Avenue Tissot 15, cp 1255, CH-1001 Lausanne (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 03/004505 A1

(54) Title: OXALIPLATIN ACTIVE SUBSTANCE WITH A VERY LOW CONTENT OF OXALIC ACID

(57) Abstract: The present invention relates to an oxaliplatin active substance for a pharmaceutical composition, wherein its weight content in oxalic acid is not more than 0.08 %, and to a process of preparing the active substance.

# Oxaliplatin active substance with a very low content of oxalic acid

The present invention relates to an oxaliplatin active substance for a pharmaceutical composition, which active substance has a very low content of oxalic acid, to a process for preparing said active substance, to the use thereof for preparing a pharmaceutical composition, in particular by dissolving thereof in an aqueous medium, and to pharmaceutical compositions thereby obtained, notably in the form of a lyophilisat formulation, a liquid formulation or a sustained release formulation for parenteral or oral administration.

Oxaliplatin (INN) or cis-oxalato(trans-*l*-1,2-diaminocyclohexane)-platinum (II) (CAS RN: 61825-94-3), is a diamine cyclohexane platinum derivative which is active in several solid tumour types such as colorectal cancers.

The molecular structure of that compound and its pharmaceutical properties were first disclosed by Kidani et al. in J. Med. Chem., 1978, 21, 1315, and in US patent No. 4,169,846. The proposed general recipe to prepare that compound leads to the compound with such a low yield that it could not be envisaged to be performed on an industrial scale. Improved methods for synthesizing oxaliplatin were then disclosed in the patent literature (see e.g. US patent Nos. 5,290,961, 5,298,642 and 5,338,874, European Patent Publications Nos. 625523 and 801070).

All these published methods of synthesis of oxaliplatin include as last step the substitution in an aqueous solution of the two aquo ligands on Pt (II) by dicarboxylate coming from oxalic acid or an oxalate salt, that step being conducted in a slight excess of oxalic acid or oxalate salt. In spite of a disclosed subsequent purification step there is some residual oxalic acid in the purified oxaliplatin.

The presence of some residual oxalic acid in the oxaliplatin active substance obtained by such methods has however never been recognized as representing a problem although its relative toxicity was well documented in the literature.

For example US Patent No. 5,290,961 and European Patent Publication No. 801070 describe processes of preparing oxaliplatin that is substantially free of impurities such as by-products containing silver ions, halogen atoms or a Pt (IV) complexes. Oxalic acid is not mentioned as an impurity.

PCT Patent Publication No. 99/43355 discloses the stabilizing effect of adding oxalic acid as a buffering agent to oxaliplatin aqueous pharmaceutical formulations.

Neurotoxicity is a severe dose-limiting side effect of oxaliplatin. F. Grolleau et al., 2001, "A possible explanation of a neurotoxic effect of anticancer agent oxaliplatin on neuronal voltage-gated sodium channels", The American Physiological Society, 2293-2297, have shown in vitro on neuronal voltage-gated sodium channels that oxalate ions, which represent a major metabolite of oxaliplatin biotransformation, may be responsible for the neurotoxicity of that compound.

The present invention is based on the unexpected discovery by the Applicant that oxaliplatin active substance which contains a very small amount of oxalic acid, e.g. a weight content of about 0.40 % or 0.20 %, has a significantly higher in vivo toxicity than oxaliplatin active substance without detectable oxalic acid or with a weight content of oxalic acid of not more 0.08 %.

The problem addressed by the invention is to find an oxaliplatin active substance and a process for preparing that active substance, wherein a pharmaceutical composition containing that active substance has a reduced toxicity.

The above problem is solved by the invention as defined in the appended set of claims.

The invention thus relates to an oxaliplatin active substance for a pharmaceutical composition, wherein its weight content in oxalic acid is not more than 0.08 %, in particular not more than 0.05 %, most preferably less than 0.02 %.

That oxaliplatin active substance may be prepared by a process close to that described in US Patent No. 5,290,961, which further includes compared to either of those processes, washing 2 to 5 times with water having a pH 4.5-7.0 the oxaliplatin crystals separated by filtration after reaction with alkali metal salt of oxalic acid, and washing 2 to 5 times the recrystallised crystals with water having a pH 4.5-7.0, the amount of water being used in those washings being sufficient for attaining the desired weight content in oxalic acid.

The invention thus also concerns a process for preparing the above-defined active substance comprising the following steps

(a) reacting in aqueous solution potassium tetrachloroplatinate $K_2PtCl_4$ with trans-*l*-1,2-cyclohexanediamine, such as to obtain dichloro(trans-*l*-1,2-cyclo-hexanediamine)-platinum (II);

(b) adding 1.6 equivalents in respect to the compound obtained in (a) of silver nitrate, such as to obtain diaquo(trans-*l*-1,2-cyclohexanediamine)-platinum (II);

(c) optionally adding to the obtained solution a catalytic amount of potassium iodide or sodium iodide, stirring and adding active carbon under stirring;

(d) filtering and adding to the obtained filtrate alkali metal salt of oxalic acid such as lithium, sodium, potassium salt, preferably potassium salt, separating

the oxaliplatin crystals formed by filtration and washing up to 5 times those crystals with water having a pH 4.5-7.0; and

(e) purifying oxaliplatin by recrystallisation wherein the crystals are collected on a filter and washed up to 5 times with water having a pH 4.5-7.0, wherein the amount of water used in washing during steps (d) and (e) is sufficient to attain the desired weight content in oxalic acid.

The person skilled in the art will readily select the appropriate volume of water having a pH 4.5-7.0 used at each washing in step (d) or step (e) in view of the desired content of oxalic acid in the oxaliplatin active substance and the acceptable yield in oxaliplatin. That volume is generally not more than 10ml per gram of active substance. The respective content of residual oxalic acid in each crop is quantified by an appropriate high performance liquid chromatography method.

The above-defined oxaliplatin active substance may be used for preparing a pharmaceutical composition useful in cancer treatment which presents a reduced toxicity compared to pharmaceutical compositions prepared using an oxaliplatin active substance of the prior art.

Generally the preparation of such a pharmaceutical composition includes the step of dissolving the active substance in an aqueous medium.

The invention is thus related to the use of the above oxaliplatin active substance for preparing a pharmaceutical composition, to a process for preparing the same comprising the step of dissolving the active substance in an aqueous medium, to a pharmaceutical composition obtainable by that process and to a new pharmaceutical composition which contains that active substance, along with pharmaceutically acceptable excipients. Due to the complex physicochemical interactions that take place in the aqueous medium, which may include dissociation to a low degree of oxaliplatin into oxalic acid and diaquo(trans-*l*-1,2-cyclohexanediamine)-platinum (II), the oxalic acid weight

content may be higher when the oxaliplatin active substance is in aqueous medium than when it is in anhydrous state.

The pharmaceutical composition may be a lyophilisate pharmaceutical formulation for parenteral or oral administration. Such a formulation is conveniently obtained by completely dissolving, at a temperature about 40 °C and under stirring, oxaliplatin in a solution of an excipient such as lactose monohydate in sterile water, then filtering once for clarification and one or more times for sterilisation, aliquoting the filtrate solution into vials and performing freeze-drying using cycles of freezing, primary drying (sublimation) and secondary drying according to techniques well known in the art.

The weight content of oxalic acid in the lyophilisate pharmaceutical formulation is preferably not more than 0.60 %, more preferably not more than 0.30 %, most preferably not more than 0.20 %.

The pharmaceutical composition may also be a liquid pharmaceutical formulation for parenteral administration. Such a formulation is generally obtained by completely dissolving oxaliplatin in sterile water, at a temperature about 40 °C and under stirring, then filtering once for clarification and one or more times for sterilisation, as described in PCT Patent Publication No. 96/04904.

The weight content of oxalic acid in the liquid pharmaceutical formulation is preferably not more than 0.60 %, more preferably not more than 0.30 %, in particular not more than 0.20 %.

The pharmaceutical composition may also be a sustained release formulation including biodegradable polymeric material, notably in the form of microparticles, microspheres, microgranules, implants or gels. Preparation of such an oxaliplatin sustained release formulation may be performed according to techniques well known in the art, with the limitation that all steps must be performed at a pH where the oxaliplatin active substance is stable, preferably

between 4,5 and 7.0. An example of an appropriate method for preparing a sustained release formulation of microspheres is the process for preparing oxaliplatin encapsulating poly(D,L-lactide-co-glycolide)/poly(D,L-lactide) (PLGA/PLA) microspheres described in PCT Patent Publication No. 02/28386.

The examples which follow will serve to better describe the invention, but are in no way to be considered as limitative.

EXAMPLE 1: Preparation of an oxaliplatin active substance with a very low content of oxalic acid by applying modifications of the method described in US Patent No. 5,290,961

562.5 g of potassium chloroplatinate and 154.8 g of trans *l*-1,2-cyclohexane-diamine were dissolved and mixed in 3.5 litres of water to obtain cake-like cis-dichloro(trans-*l*-1,2-cyclohexanediamine)-platinum (II) without recrystallisation. The latter compound was suspended in 5.7 litres of water to which was added a solution which had been prepared by dissolving 386.4 g of silver nitrate in 2.8 litres of water. After this solution was stirred in the dark at room temperature for three days, most of the precipitate of silver chloride was removed by filtration. After the filtrate was concentrated under reduced pressure, a solution consisting of 45 ml of water and 3.85 g of potassium iodide dissolved therein was added followed by one hour stirring, and then active carbon was added. Silver iodido and iodine compounds then formed and the active carbon were completely removed by filtration. To the remaining filtrate was added 299.4 g of potassium oxalate monohydrate which was allowed to stand for two hours to obtain crude crystals of desired cis-oxalate (trans *l*-1,2-cyclohexanediamine)-platinum (II) which were collected by filtration and washed twice with 200 ml of sterile water of pH 5.9. Then, 65g of this crude crystal was dissolved under heating in 2.7 litres of water, filtered and cooled to room temperature. The platinum crystals precipitated were collected by filtration and washed four times with 150 ml of water of pH 6.5. The crystals obtained were dried thereby yielding 30 g of oxaliplatin active substance.

The weight content of oxalic acid in the oxaliplatin active substance was determined using a hereafter briefly described specific ion-pair reverse phase HPLC test which has a detection limit of 0.02 w/w % for oxalic acid.

The test solution consists of oxaliplatin dissolved using sonication at the concentration of 2 mg/ml in water. The specific ion-pair reverse phase HPLC test is conducted at pH 6.0 ± 0.05 and a temperature of 40 °C on a glass column of diameter 4.6 mm and length 25 cm containing a base-deactivated octadecylsilyl silica gel for chromatography, with a mobile phase consisting of 20 volumes of acetonitrile and 80 ml of a solution prepared by adding 1.36 g potassium dihydrogen phosphate to 10 ml 0.4 M tetrabutylammonium hydroxide and adjusting the pH to 6.0 ± 0.05 with phosphoric acid, a flow rate of 2 ml / minute and UV detection at 205 nm.

No oxalic acid was detected, corresponding to a weight content of oxalic acid below w/w 0.02 % for the oxaliplatin active substance.

EXAMPLE 2 (Comparative example) Preparation of an oxaliplatin active substance according to one of the methods described in EP Patent Application No. 625523

Potassium tetrachloroplatinate (3.40 g) was stirred at room temperature with trans-*l*-1,2-cyclohexanediamine (0.94 g) in aqueous solution (80 ml). The clear orange solution present at the onset of the reaction rapidly turned yellow with a precipitate beginning to form after 30 minutes. The reaction mixture was stirred overnight (14 hours) and filtered. The yellow precipitate was washed with water and dried under vacum. The crude obtained product (2.98 g) was recrystallised from 6 litres of boiling 0.1N HCl. Upon cooling to room temperature, crystals of dichloro-(trans-*l*-1,2-cyclohexanediamine)-platinum (II) (2.33 g) were collected by filtration. In parallel, an aqueous solution of oxalic acid (1.29 g, in 10 ml of water) was added dropwise to an aqueous suspension of silver carbonate (2.64 g, in 10 ml of water). Upon stirring 15 minutes at room temperature, carbon dioxide evolution ceased, suggesting a quantitative formation of silver

oxalate. The off-white precipitate was collected by filtration. The filtrate was washed abundantly with water and dried under vacum. To an aqueous suspension of dichloro (trans-*l*-1,2-cyclohexanediamine)-platinum (II) (1.5 g, in 120 ml of water) as obtained above, silver oxalate (1.199 g) was added as a solid and stirred for 4 hours at room temperature in the dark. With time, the yellow suspension became paler. The precipitate silver chloride was removed by filtration. The resulting clear solution was concentrated to 15 ml to yield a yellow precipitate. After standing at room temperature for 1 hour, the pale yellow precipitate was collected by filtration, yielding to cis-oxalato (trans-*l*-1,2-cyclohexane-diamine)-platinum (II).

A sample has been analysed by applying the above-described HPLC method and oxalic acid was detected, corresponding to a weight content of oxalic acid of w/w 0.19 % for the oxaliplatin active substance.

EXAMPLE 3: Preparation of a pharmaceutical composition in the form of a liquid formulation for parenteral administration using the oxaliplatin active substance of the invention

In a glass or inox container equipped with a thermostat, about 80 % of the desired sterile water are introduced and the temperature is brought under stirring (800-1200 rpm) to a temperature of 40 ± 5 °C.

The amount of oxaliplatin active substance (as obtained in Example 1) necessary to obtain a final concentration for example of 5 mg / ml is separately weighed, then added in preheated sterile water to the sterile water in the glass or inox container. The weighing container is rinsed three times with sterile water, the rinsing solution being added to the above mixture. The latter is stirred at the above temperature during 30 to 60 minutes, until complete dissolution of oxaliplatin. Optionally the water is bubbled with nitrogen to lower its oxygen content.

The volume or weight of the solution is adjusted to its desired value by adding sterile water. The solution is stirred at 40 ± 5 °C during about 10 minutes then cooled to 30 °C under stirring. Samples of the solution are then collected for the usual control tests. The solution is then subjected to aseptic filtration on a 0.2 μm membrane or alternatively autoclaving under conditions close to those described in European Pharmacopia 1997 Edition page 283-284 (minimum of 121 °C for 15 minutes). The solution is kept at 15-30 °C before being conditioned.

The oxaliplatin solution for example at 5 mg/ml is then aseptically and preferably under nitrogen atmosphere conditioned in 5 ml cylindrical vials (volume of added solution about 4 ml corresponding to 20 mg available oxaliplatin), 15 ml cylindrical vials (volume of added solution about 10 ml corresponding to 50 mg available oxaliplatin), and 25 ml cylindrical vials (volume of added solution about 20 ml corresponding to 100 mg available oxaliplatin).

Those vials are kept during 12 months partly in an incubator at 25 °C and a relative humidity of 60 % and partly in an incubator at 40 °C and a relative humidity of 75 %.

EXAMPLE 4 *Preparation of a pharmaceutical composition in the form of a* lyophilisate for parenteral administration using the oxaliplatin active substance of the invention.

In a glass or inox container equipped with a thermostat, about 80 % of the desired sterile water are introduced and the temperature is brought under stirring (800-1200 rpm) to a temperature of 38 ± 5 °C. Lactose monohydrate is added under stirring until a final concentration of 45 mg / ml.

The amount of oxaliplatin active substance (as obtained in Example 1) necessary to obtain a final concentration for example of 5 mg/ml is separately weighed, then added in preheated sterile water to the sterile water in the glass

or inox container. The weighing container is rinsed three times with sterile water, the rinsing solution being added to the above mixture. The latter is stirred at the above temperature during 30 to 60 minutes, until complete dissolution of oxaliplatin. Optionally the water is bubbled with nitrogen to lower its oxygen content.

The volume or weight of the solution is adjusted to its desired value by adding sterile water. The solution is stirred at 40 ± 5 °C during about 10 minutes then cooled to 15-30 °C under stirring. Samples of the solution are then collected for the usual control tests. The solution is subjected to aseptic filtration on a 0.2 μm membrane; then aseptically filled into 50 ml cylindrical vials to give 100 mg oxaliplatin per vial. Freeze-drying is performed using cycles of freezing, primary drying (sublimation) and secondary drying, according to techniques well known in the art. The vials containing the lyophilisate pharmaceutical formulation are stoppered and sealed.

EXAMPLE 5: Evaluation of the relative toxicity due to the presence of oxalic acid in oxaliplatin active substance - Determination of lethal doses $LD_{10}$

Lethal doses $LD_{10}$ of a cytostatic active substance determinated in mice is generally considered as being a significative correlation with the maximum tolerated doses (MTD) in man.

Accordingly, a first group of CD-1 mice has received a solution of the oxaliplatin active substance as obtained in Example 1 and $LD_{10}$ is around 18.0 mg7kg.

A second group of animals has received the same solution as for the first group, but with the addition of oxalic acid at a final concentration of 0.2 mM, and $LD_{10}$ is around 14.4.

Finally, a control group has only received a solution of oxalic acid at a concentration of 0.2 mM and no significant toxicity has been observed.

LD10 along with clinical symptoms demonstrate that the oxaliplatin active substance as obtained in Example 4, while administrated in solution, is less toxic as the same active substance, but administrated with oxalic acid.

5

## Claims

1. Oxaliplatin active substance for a pharmaceutical composition, wherein its weight content in oxalic acid is not more than 0.08 %.

2. Active substance of claim 1 wherein its weight content in oxalic acid is not more than 0.05 %, in particular less than 0.02 %.

3. Process of preparing the active substance of claim 1 or 2 comprising the following steps

(a) reacting in aqueous solution potassium tetrachloroplatinate $K_2PtCl_4$ with trans-l-1,2-cyclohexanediamine, such as to obtain dichloro(trans-l-1,2-cyclohexanediamine)-platinum (II),

(b) adding two equivalents in respect to the compound obtained in (a) of silver nitrate, such as to obtain diaquo(trans-l-1,2-cyclohexanediamine)-platinum (II),

(c) optionally adding to the obtained solution potassium iodide or sodium iodide, stirring and adding active carbon under stirring,

(d) filtering and adding to the obtained filtrate alkali metal salt of oxalic acid, separating the oxaliplatin crystals formed by filtration and washing 2 to 5 times those crystals with water having a pH 4.5-7.0, and

(e) purifying oxaliplatin by recrystallisation wherein the crystals are collected on a filter and washed 2 to 5 times with water having a pH 4.5-7.0, wherein the amount of water used in washing during steps (d) and (e) is sufficient to attain the desired weight content in oxalic acid.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH 02/00358

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F15/00 A61K31/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 4 169 846 A (INAGAKI KENJI ET AL)<br>2 October 1979 (1979-10-02)<br>cited in the application<br>* see the elemental analysis data of compounds 4-6 *<br>column 11 -column 12; table 4<br>--- | 1-3 |
| X | EP 0 943 331 A (SANOFI SA)<br>22 September 1999 (1999-09-22)<br>cited in the application<br>page 10, line 10 - line 20<br>--- | 1,3 |
| X | WO 00 21527 A (DEBIOPHARM SA ;MAUVERNAY ROLLAND YVES (CH))<br>20 April 2000 (2000-04-20)<br>page 7; table 1<br>---<br>-/-- | 1-3 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 31 October 2002 | 07/11/2002 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Rinkel, L |

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH 02/00358

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0 625 523 A (TANAKA PRECIOUS METAL IND)<br>23 November 1994 (1994-11-23)<br>cited in the application<br>whole document, in particular page 11;<br>example 9<br>--- | 1-3 |
| A | WO 96 04904 A (DEBIOPHARM SA ;IBRAHIM HOUSSAM (CH); MAUVERNAY ROLLAND YVES (CH))<br>22 February 1996 (1996-02-22)<br>cited in the application<br>page 2<br>page 6 -page 9; examples 1-3<br>--- | 1-3 |
| L | DATABASE CA 'Online!<br>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;<br>ZHU, Y. P. ET AL: "Studies on a sustained-release procainamide hydrochloride tablet - an oral osmotic pump"<br>retrieved from STN<br>Database accession no. 110:141424<br>XP002181632<br>abstract<br>& YAOXUE XUEBAO (1988), 23(11), 850-6,<br>--- | |
| L | DATABASE CA 'Online!<br>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;<br>BRADBROOK, I. D. ET AL: "Comparison of pharmacokinetic profiles of single and multiple doses of a slow release Oros oxprenolol delivery system in young normotensive and elderly hypertensive subjects"<br>retrieved from STN<br>Database accession no. 105:29910<br>XP002181633<br>abstract<br>& BR. J. CLIN. PHARMACOL. (1986), 21(4), 371-6,<br>----- | |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CH 02/00358

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 4169846 A | 02-10-1979 | JP 1314396 C | 28-04-1986 |
| | | JP 53031648 A | 25-03-1978 |
| | | JP 60041077 B | 13-09-1985 |
| EP 0943331 A | 22-09-1999 | AT 202472 T | 15-07-2001 |
| | | AU 2632499 A | 15-09-1999 |
| | | BR 9908273 A | 24-10-2000 |
| | | CN 1291886 T | 18-04-2001 |
| | | DE 69900162 D1 | 02-08-2001 |
| | | DE 69900162 T2 | 18-04-2002 |
| | | DK 943331 T3 | 15-10-2001 |
| | | EP 0943331 A2 | 22-09-1999 |
| | | ES 2161085 T3 | 16-11-2001 |
| | | WO 9943355 A2 | 02-09-1999 |
| | | GR 3036646 T3 | 31-12-2001 |
| | | HU 0103707 A2 | 28-02-2002 |
| | | JP 2002504524 T | 12-02-2002 |
| | | NO 20004240 A | 18-10-2000 |
| | | PL 343021 A1 | 30-07-2001 |
| | | PT 943331 T | 28-12-2001 |
| | | US 6306902 B1 | 23-10-2001 |
| | | ZA 9901489 A | 30-09-1999 |
| WO 0021527 A | 20-04-2000 | AT 218337 T | 15-06-2002 |
| | | AU 5880799 A | 01-05-2000 |
| | | BR 9914508 A | 30-10-2001 |
| | | CA 2346564 A1 | 20-04-2000 |
| | | DE 69901725 D1 | 11-07-2002 |
| | | EP 1121117 A2 | 08-08-2001 |
| | | WO 0021527 A2 | 20-04-2000 |
| EP 0625523 A | 23-11-1994 | JP 3025602 B2 | 27-03-2000 |
| | | JP 6329692 A | 29-11-1994 |
| | | DE 69331048 D1 | 06-12-2001 |
| | | DE 69331048 T2 | 21-03-2002 |
| | | EP 0625523 A1 | 23-11-1994 |
| | | ES 2167328 T3 | 16-05-2002 |
| | | US 5420319 A | 30-05-1995 |
| WO 9604904 A | 22-02-1996 | AT 197249 T | 15-11-2000 |
| | | AU 2989695 A | 07-03-1996 |
| | | BR 9508554 A | 25-11-1997 |
| | | CA 2196922 A1 | 22-02-1996 |
| | | CZ 9700379 A3 | 11-06-1997 |
| | | DE 69519300 D1 | 07-12-2000 |
| | | DE 69519300 T2 | 31-05-2001 |
| | | DK 774963 T3 | 29-01-2001 |
| | | EP 0774963 A1 | 28-05-1997 |
| | | ES 2152412 T3 | 01-02-2001 |
| | | WO 9604904 A1 | 22-02-1996 |
| | | IL 114852 A | 29-02-2000 |
| | | JP 10508289 T | 18-08-1998 |
| | | RU 2148400 C1 | 10-05-2000 |
| | | US 5716988 A | 10-02-1998 |